REMARKS

Entry of the foregoing and reexamination of the above-identified application is respectfully requested.

Claim 24 has been deleted without prejudice or disclaimer as being directed to a non-elected invention. Applicants reserve the right to file a divisional application directed to this claim.

The specification has been objected to for not identifying by the sequence in the sequence listing "RHHHGP[G]." Applicants are in the process of obtaining a revised sequence listing to include that sequence. Upon receipt, the specification will be amended and the sequence listing submitted. It is respectfully requested that this objection be held in abeyance until receipt of the revised sequence listing.

Claim 4 has been amended to recite that "no" more than 200 amino acid residues are present in the peptide of interest. Withdrawal of the objection to claim 4 is respectfully requested and believed to be in order.

Claims 1-23 and 25-27 have been rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter not described in the specification. This rejection is respectfully traversed.

The Official Action asserts that the claims encompass a genus of peptides, including GLP-1, while the specification discloses only three species of the genus. The specification is also said to fail to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a GLP-1 derivative,

and does not provide any structure/function correlation for members of the claimed genus. These assertions are in error.

The present invention as recited in claim 1, for example, is not directed to a process for production of a *particular* peptide. The present invention is directed to a *particular* process which can be used for production of *any* peptide. As recited in claim 1, the peptide of interest is expressed as an intermediate peptide comprising the peptide of interest and a helper peptide which is added to the peptide of interest. In this intermediate peptide (or precursor peptide) the helper peptide changes physicochemical properties of the peptide of interest so that the intermediate (or precursor) peptide can be easily, and stably purified. After purification of the intermediate peptide, the intermediate peptide is cleaved to liberate the peptide of interest. This method is not restricted to a particular peptide of interest, but instead can be generally used by those skilled in the art for any peptide or interest. This would be clear to a person skilled in the art. The assertion in the Official Action that the claims encompass a genus comprising a peptide of not limited by structure is thus correct. However, that does not mean that the written description requirement is not met. The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter. In re Kaslow, 217 USPQ 1059, 1076 (Fed. Cir. 1983). Ex parte Remark, 15 USPQ2d 1498, 1506 (PBAI 1990).

Compliance with the written description requirement of §112 only requires that the application contain sufficient disclosure, expressly or inherently, to make it clear to persons

skilled in the art that applicant possessed the subject matter claimed. Ex Parte Harvey, 3 USPQ2d 1626, 1627 (PBAI 1987). A specification may, within the meaning of 35 U.S.C. §112, 1st para., contain a written description of a broadly claimed invention without describing all species. Utter v. Hiraga, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988).

Thus, the fact that not all peptides of interest which could be used in the claimed method does not mean that the written description requirement has not been met. The method is disclosed in the specification as being applicable to peptides of interest generally. *See, e.g.,* page 5, line 6 - page 6, line 17. GLP-1 is given as an *example* of a peptide of interest. *See, e.g.,* page 2, lines 20-25. The claimed method is used to overcome general problems in the art, not problems related to specific peptides of interest. The problems are, *for example*, "problems of solubility and gelling of the peptide of interest under various conditions of cleavage and modification reactions, the problem of sample concentration to be loaded on the column during the column chromatographic process, the problem of the elution conditions from the column and the stability after elution, and the like." Page 10, lines 4-15. The structure or identification of the particular peptide of interest does not cause the particular problems being overcome and is not important for the claimed method.

The specification in fact identifies many peptides which can be used as the peptide of interest for the present invention, *for example,* on page 10, line 34 - page 11, lines 1 to 27:

> In addition to the above-mentioned GLP-a derivatives, the peptides of interest that can be produced according to the present invention include, but are not limited to, the peptides comprising not greater than 200 amino acid residues.

Examples of such peptides include adrenocorticotropic hormone, adrenomedullin, amylin, angiotensin I, angiotensin II, angiotensin III, A-type natriuretic peptide, B-type natriuretic peptide, bradykinin, big gastrin, calcitonin, calcitonin gene related peptide, cholecystokinin, corticotropin releasing factor, cortistatin, C-type natriuretic peptide, defesin 1, delta sleep-inducing peptide, dynorphin, elafin, α-endorphin, β-endorphin, γ-endorphin, endothelin-1, endothelin-2, endothelin-3, big endothelin-1, big endothelin-2, big edothelin-3, enkephalin, galanin, gib gastrin, gastrin, gastric inhibitory polypeptide (GIP), gastrin releasing peptide, glucagon, glucagon-like peptide-2, growth hormone releasing factor, growth hormone, guanylin, uroguanylin, histatin 5, insulin, joining peptide, luteinizing hormone releasing hormone, melanocyte stimulating hormone, midkine, motilin, neurokinin A, neurokinin B, neuromedin B, meuromedin C, neuropeptide Y, neurotensin, oxytocin, proadrenomedullin N-terminal 20 peptide, cromogranin A, parathyroid hormone, PTH related peptide, peptide histidine-methionine-27, pituitary adenylate cyclase activating polypeptide 38, platelet factor-4, peptide T, secretin, serum thymic factor, somatostatin, substance P, thyrotropin releasing hormone, urocortin, vasoactive intestinal peptide, vasopressin, and the derivatives thereof, etc.

Thus, the genus of peptides of interest which can be used in the instant invention are fully described in the specification.

With respect to GLP-1 and derivatives thereof, such peptides are well known in the art. The specification specifically identifies Bell et al, *Nature*, 304:368-71 (1983), and Jojsow et al, *J. Clin. Invest.* 79:616-19 (1987) as examples of descriptions of such peptides. Page 2, lines 20-32. Many GLP-1 derivatives are also identified on page 11, line 28 to page 14, line 2. GLP-1 is thus a well known peptide, and many GLP-1 derivatives are also well known. *See also,* the enclosed U.S. Patent Nos 5,118,666 and 5,545,618. In addition, the general description of GLP-1 derivatives would show possession of such compounds since GLP-1 derivatives are readily produced by well-known conventional procedures such as cite-directed mutagenesis, etc. *See, for example,* Sambrook et al, *Molecular Cloning*, a Laboratory Manual, Second Edition, Article 15.

In addition, the specification describes the physicochemical properties to be considered to select combinations of peptides of interest and helper peptides. *See,* page 5, lines 6-15.

In view of the above, it is respectfully believed that the peptides to be used in the claimed method are fully described in the specification. One skilled in the art would clearly recognize that the inventors were in possession of the invention as claimed based upon the description. Withdrawal of this rejection of record is respectfully requested. Such action is believed to be in order.

Claims 1-23 and 25-27 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification. This rejection is respectfully traversed.

According to the Official Action, the specification enables a process of making only GLP-1 (7-37). The claims allegedly are directed to a genus of a polypeptide of unknown function or retaining insulinotropic activity, and the breadth of the claims is allegedly broader than the disclosure.

As stated *supra*, the claimed method is applicable to peptides of interest generally. *See, e.g.,* page 5, line 6 - page 6, line 17. GLP-1 is given as an *example* of a peptide of interest. *See, e.g.,* page 2, lines 20-25. The claimed method is used to overcome general problems in the art, not problems related to specific peptides of interest. The structure or identification of the particular peptide of interest does not cause the particular problems being overcome and is not important for the claimed method. The specification in fact identifies many peptides which can be used as the peptide of interest for the present invention, *for example,* on page 10, line 34 - page 11, lines 1 to 27.

As shown by the specification, the process is in fact applicable to various different peptides of interest. No undue experimentation would be necessary for one skilled in the art to practice the claimed process.

In addition, the specification describes the physicochemical properties to be considered to select combinations of peptides of interest and helper peptides. *See,* page 5, lines 6-15. By using these teachings, the claimed method could be practice by one skilled in the art. No undue experimentation would be necessary.

In view of the above, the claimed invention is enabled by the specification. Withdrawal of the rejection under §112 is respectfully requested. Such action is believed to be in order.

Claims 1-23 and 25-27 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is respectfully traversed in part and is rendered moot in part.

Claim 1 has been rewritten to delete step (3) where the peptide of interest is modified versus the peptide not being modified. New claim 28 has been added to recite that the peptide of interest obtained in step (2) is modified.

With respect to "GLP-1 derivative" in claims 14-17, it is believed that the phrase would be sufficiently clear to a person skilled in the art. The specification lists many GLP-1 derivatives on page 11, line 28 to page 14, line 2. The GLP-1 is a well known peptide, and many GLP-1 derivatives are also well known. *See also,* the enclosed U.S. Patent Nos. 5,118,666 and 5,545,618. In addition, GLP-1 can be modified by well-known

conventional procedures such as cite-directed mutagenesis, etc. See, for example, Sambrook et al, *Molecular Cloning*, a Laboratory Manual, Second Edition, Article 15.

It is thus believed that the language used in the claims would be sufficiently definite when read in light of the specification.

Regarding claim 23, sufficient antecedent basis is now present in the claim for "endotoxin" in line 2.

Claims 1-13, 18-23 and 25-27 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Tarnowski et al. Claims 1-13, 18-23 and 25-27 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Yabuta et al. These rejections are respectfully traversed.

Tarnowski et al is said to teach a method for expressing peptides as fusion proteins having a high pI (*see,* Abstract, col. 1, ll. 40-58, claims 1-8). Yabuta et al is said to teach a method for expressing peptides as fusion proteins having as a protective peptide *E. coli* β-galactosidase. Tarnowski et al and Yabuta et al both describe a process of production of a peptide. In these methods, a fusion protein comprising (1) a peptide of interest and (2) a carrier protein is expressed, and the peptide of interest is directly liberated from the fusion protein by the cleavage of the fusion protein. Such a method neither discloses nor suggests applicants' claimed method. By contrast with Tarnowski et al and Yabuta et al, according to the present invention, a fusion protein comprising (1) a peptide of interest, (2) a helper peptide and (3) a carrier protein is expressed. Next, the fusion protein is cleaved to liberate an intermediate (precursor) peptide comprising (1) the peptide of interest and (2)

the helper peptide, and the liberated intermediate peptide is purified. After that, the intermediate peptide is cleaved so as to liberate (1) the peptide of interest.

By using these steps of the instantly claimed invention, the problems possessed by the protein of interest, such as insolubility of the peptide, gel-formation, etc., during purification and other downstream processing, are overcome. The cited references do not describe these problems in the art, nor a means for solution to overcome them.

By failing to describe or even suggest the use of a helper and carrier protein, as well as a process wherein an intermediate peptide comprising the peptide of interest and a helper peptide are purified and then cleaved to liberate the peptide of interest, Tarnowski et al and Yabuta et al fail to anticipate the claimed invention.

Withdrawal of the rejections of the claims under §102(b) is respectfully requested and believed to be in order.

Claims 14-17 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Tarnowski et al in view of Bell et al. Claims 14-17 have also been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Yabuta et al in view of Bell et al. These rejections are respectfully traversed.

Bell is cited as teaching GLP-1. It allegedly would have been obvious to use the method of Tarnowski et al or Yabuta et al to express GLP-1. As stated *supra*, neither Tarnowski et al nor Yabuta et al disclose or suggest a method as claimed wherein a fusion protein comprising (1) a peptide of interest, (2) a helper peptide and (3) a carrier protein is expressed, and wherein the fusion protein is cleaved to liberate an intermediate (precursor) peptide comprising (1) the peptide of interest and (2) the helper peptide, and the liberated

intermediate peptide is purified, followed by a step wherein the intermediate peptide is cleaved so as to liberate (1) the peptide of interest.

The teachings in Bell of GLP-1 together with the teachings of Tarnowski et al and Yabuta et al thus fail to teach or even suggest the instantly claimed methods wherein GLP-1 is the peptide of interest.

Withdrawal of the rejections of the claims under §103(a) is respectfully requested and believed to be in order.

Further and favorable action in the form of Notice of Allowance is respectfully requested. Such action is believed to be in order.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney be telephone at 508-339-3684 so that prosecution would be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Elin M. #51,147
for: Donna M. Meuth
Registration No. 36,607

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620
Date: April 10, 2002

Attachment to Reply and Amendment dated April 10, 2002

Marked-up Claims 1, 4 and 23

1. (Amended) A process for producing a peptide having a desired biological activity, comprising the steps of:

(1) culturing cells transformed with an expression vector having the nucleotide sequence encoding a peptide of interest that has a helper peptide added thereto, or a fusion protein that has a protective peptide further added to the peptide of interest that has a helper peptide added thereto; and then harvesting said peptide of interest that has a helper peptide added thereto or said fusion protein from said culture;

(2) in the case wherein a fusion protein is obtained in step (1), cleaving off from said fusion protein the peptide of interest that has a helper peptide added thereto and the protective peptide, and purifying the peptide of interest that has a helper peptide added thereto as desired;

(3) [in the case wherein modification is required from the peptide of interest, subjecting the peptide of interest that has a helper peptide added thereto obtained in step (1) or step (2) to a modification reaction;

(4)] cleaving off from the peptide of interest that has a helper peptide added thereto obtained in step (1) [,] or step (2) [or step (3)], the helper peptide and the peptide of interest, and purifying the peptide of interest as desired; and

[(5)] (4) purifying the peptide of interest obtained in step [(4)] (3).

Attachment to Reply and Amendment dated April 10, 2002

Marked-up Claims 1, 4 and 23

4. (Twice Amended) The process according to claim 1, wherein said peptide of interest has [not] no more than 200 amino acid residues.

23. (Twice Amended) The process according to claim 1, wherein endotoxin is present in the final purified product, and wherein the content of endotoxin in the final purified product is not greater than 0.03 units/mg.